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[Intervention Review]

Phosphodiesterase 5 inhibitors for pulmonary hypertension

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ABSTRACT

Background

Pulmonary Hypertension (PH) can be either of unknown aetiology (primary pulmonary hypertension (PPH)) or due to a known underlying cause (secondary pulmonary hypertension (SPH). Pulmonary arteriolar vasoconstriction is considered to be an important characteristic of PH. Therapies which aim to vasodilate are used to treat pulmonary hypertension.

Objectives

To determine the clinical efficacy of sildenafil, a vasodilator which works through inhibition of the enzyme phosphodiesterase type V (PDE5I), administered via any route to people with pulmonary hypertension in primary or secondary forms.

Search methods

MEDLINE, EMBASE and CENTRAL were searched with pre-defined search terms. Searches were current as of October 2006.

Selection criteria

Randomised controlled trials were considered for inclusion in the review. We included studies which assessed the effects of sildenafil in participants with PPH and SPH.

Data collection and analysis

Two reviewers independently assessed and extracted data from clinical trials. Data were entered in RevMan Analyses 1.0.2. Continuous data were pooled with an estimate on either WMD (weighted mean difference) or SMD (standardised mean difference) scales. Dichotomous data were pooled and a RR (relative risk) was calculated.

Main results

Four studies recruiting 77 participants met the inclusion criteria of the review. Two studies assessed the acute effects of sildenafil. Two small crossover study assessed the effects of long term administration. The 'acute effect' studies indicated that sildenafil has a pulmonary vasodilatory effect. The two crossover studies showed improvement in symptoms. One study showed improvement in fatigue domains from a validated health status questionnaire. Both crossover studies reported that the drug was well tolerated.

Authors' conclusions

The validity of the observed effects is undermined by small participant numbers and inadequate exploration of the different disease etiologies. The effects on long term outcome such as NYHA functional class, symptoms, mortality and exercise capacity require further

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validation. More studies of adequate size are required before the long term effects of sildenafil on clinically important outcomes can be established.

PLAIN LANGUAGE SUMMARY

Phosphodiesterase 5 (sildenafil) inhibitors for pulmonary hypertension

Pulmonary hypertension (PH) is high blood pressure in the lung circulation. It can occur without a known cause, or it can be caused by another lung disease or be secondary to abnormalities in the left side of the heart. The review sought to determine whether there was evidence that sildenafil (also known as Viagra), a drug which opens up the arteries and increases the flow of blood, could decrease pulmonary artery blood pressure and alleviate symptoms of PH. A limited number of studies of short term i duration indicated that the drug can open up the arteries. One small longer-term study found some favourable effects in terms of symptoms, but in the absence of longer term outcomes, we could not establish whether this meant that the people given the drug felt that their levels of daily activity were better. Future studies should be longer in duration, and should measure the impact of treatment on daily activities, mortality, quality of life and exercise capacity.

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BACKGROUND

Pulmonary artery hypertension is characterised by resting mean pulmonary artery pressure of greater than 25 mm Hg. This can be divided into primary where there is no demonstrable cause identified and secondary where there are underlying causes.

Primary pulmonary hypertension (PPH) is a disease of unclear aetiology. It is sporadic and a familial predisposition has been observed in 10% of the cases. Observation suggests that pulmonary arteriolar vasoconstriction plays an important role in the pathogenesis of PPH, characterised by pathologic demonstration of medial hypertrophy, impaired pulmonary vascular endothelial production of the vasodilator prostacyclin and nitric oxide and increased pulmonary vascular endothelial production of the vasoconstrictor endothelin.

The main symptoms of PPH are exertional dyspnoea, exertional chest pain, syncope, and oedema. Mean age upon diagnosis of PPH is 36 years.

Secondary pulmonary hypertension is mainly due to chronic hypoxaemia, parenchymal lung disease, chronic thromboembolic disease, left sided valvular or myocardial disease, congenital heart disease and systemic connective tissue disease.

Until now the efficacy of pulmonary vasodilator therapy has been limited due to the lack of potency and lack of selectivity, as almost all pulmonary vasodilators are also systemic vasodilators. Thus apparent benefits on the pulmonary circulation may be merely due to decreased venous blood return and decreasing right ventricular stroke output. Currently available proven therapeutic interventions for PPH include anticoagulation, vasodilators such as calcium channel blockers, epoprostenol infusion (prostacyclin analogue), nitric oxide, and lung transplantation. A Cochrane review examining the efficacy of prostacyclin has shown it to confer at least a short-term benefit (Paramothayan 2004).

Nitric oxide (NO) is a potent, short acting vasodilator. Within the vascular smooth muscle it activates soluble guanylate cyclase, which generate cGMP, which in turn relaxes smooth muscle. cGMP is degraded by phosphodiesterase (PDE). Sildenafil is a potent and selective inhibitor of PDE-5, best known for its use as a treatment for male erectile dysfunction (Viagra). In addition to its high concentration in the corpora cavernosa, PDE-5 is abundant in the vascular, tracheal and visceral smooth muscle and in platelets. The work so far with PDE-5 inhibitors have shown improved haemodynamics in pulmonary hypertension.

The reviewers intend to summarise the evidence currently published concerning the use of sildenafil in pulmonary hypertension.

OBJECTIVES

To determine the efficacy of sildenafil in the treatment of patients with pulmonary hypertension.

METHODS

Criteria for considering studies for this review

Types of studies

Randomised, double blind or single blind, placebo controlled studies were included.

Types of participants

Adult and paediatric subjects with a diagnosis of pulmonary hypertension who require medical treatment for their condition. All patients had to be anticoagulated. We included studies where mean PAP was 25> mm Hg.

Studies were included if diagnosis was based on clinical findings, pulmonary and cardiac imaging and ideally pulmonary angiograms.

Studies which included subjects with severe current other diagnoses were excluded.

Types of interventions

The following interventions have been included.

- Sildenafil versus placebo
- Sildenafil versus prostacyclin
- Sildenafil + prostacyclin versus prostacyclin alone
- Sildenafil + inhaled NO (nitric oxide) versus inhaled NO alone
- High dose versus low dose sildenafil

Any route of administration of sildenafil was considered, such as oral, IV and inhalation. Any co-intervention was acceptable. Studies of any duration were considered.

Types of outcome measures

Primary outcomes

Improvement in NYHA functional class status

Secondary outcomes

1. Haemodynamics including CO, PA pressure, others
2. Gas exchange, ABG
3. Exercise capacity
4. Quality of life/ Health status
5. Dyspnoea score
6. Mortality
7. Hospitalisation/intervention
8. Adverse events

Search methods for identification of studies

Electronic searches

Searches with pre-defined terms were conducted on MEDLINE (1966-Sept 2005, Appendix 1); EMBASE (1980- Sept 2005, Appendix 2), and the Cochrane Central Register of Controlled Trials (CENTRAL Issue 3,2005, Appendix 3) for relevant trials.

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Searching other resources

Hand searches of abstracts from meetings of ATS, BTS and ERS were conducted. Drug companies were contacted for relevant trial data where appropriate.

Data collection and analysis

Selection of studies

All trials which appeared to fit the criteria for inclusion were identified for full review by two reviewers (PK and TL).Two reviewers (PK and TL) independently selected trials for inclusion in the review. Disagreement was resolved by discussion between the two reviewers.

Selection of studies

All trials which appeared to fit the criteria for inclusion were identified for full review by two reviewers (PK and TL).Two reviewers (PK and TL) independently selected trials for inclusion in the review. Disagreement was resolved by discussion between the two reviewers.

Data extraction and management

Two authors independently assessed studies for inclusion in the review. Data were extracted and entered into Review Manager software.

Assessment of risk of bias in included studies

We assessed the risk of bias for each study in terms of allocation, blinding and other sources of bias relating to treatment or population recruited. The domains we used as the basis for this assessment (allocation generation, allocation concealment, and blinding) were judged to be at low, high or unclear risk of bias.

Data synthesis

For continuous data variables (e.g. blood pressure) a weighted mean difference was calculated by pooling the data from different studies together, where a common metric had been used. A standardised mean difference was calculated where studies had measured the same outcome but with different metrics (e.g. L/min and % predicted). We pooled data using a Fixed Effect model.

For dichotomous variables (e.g. side effects), an Odds Ratio (OR) was calculated based on the event rate data in the studies. Data were pooled using a Fixed Effect model.

Heterogeneity was tested using the I^2 statistic, which measures the extent of heterogeneity not attributable to the play of chance. Where the statistic exceeds 20% Random Effects modelling was applied to see if the results altered.

Limited meta-analysis prevented the investigation of heterogeneity when the trials were combined. In anticipation of future studies meeting the inclusion criteria of this review, heterogeneity will be explored where the I^2 statistic reaches 20%. Attempts will be made explore the differences based on the clinical characteristics of the included studies. Clinically dissimilar studies will not be statistically combined. However, when a group of studies with heterogeneous results appear to be clinically similar, the pooled effect estimates will be combined using both Fixed and Random effect models, and differences between the two types of modelling (if any) will be reported.

Subgroup analysis and investigation of heterogeneity

Possible subgroup analyses include:

1. Primary versus secondary pulmonary hypertension (where data are reported separately) .
2. Adults > 18 versus children < 18 years.
3. Route of administration of sildenafil such as oral, IV and inhalation.
4. Dosage of sildenafil (high versus low).

RESULTS

Description of studies

Results of the search

Electronic searches yielded a total of 193 references. Of these we retrieved 19 studies that were potentially relevant. One study was identified from a search of PubMed in May 2004. Four studies met the inclusion criteria (Bharani 2003; Ghofrani 2002; Ghofrani 2002a; Sastry 2004). Sixteen studies failed to meet the inclusion criteria (review articles: N = four; before and after studies: N = six; RCTs not assessing sildenafil: N = two; retrospective analysis: N = one; animal studies: N = one; observational studies: N = one; correspondence: N = one). For details of these studies, please see "Characteristics of Excluded Studies". An update search was conducted in October 2005, in which 286 references were retrieved. Of these eight were obtained for full scrutiny but none met the inclusion criteria (see Table 1).

Included studies

Study design

All included studies were randomised. Two studies had a parallel open label design (Ghofrani 2002; Ghofrani 2002a). Sastry 2004 and Bharani 2003 were double-blind crossover studies.

Participants

Participants suffered from a mixture of PPH and secondary PH in Ghofrani 2002, and suffered from PH secondary to lung fibrosis in Ghofrani 2002a. Sastry 2004 recruited participants with PPH. Bharani 2003 recruited participants with PH of varied etiologies. In the two parallel studies, participants were classified as being in either NYHA class III or IV. In Bharani 2003 and Sastry 2004, participants were classified as being in NYHA class II or above. Mean PAP in the short-term studies suggested that participants were suffering from particularly severe forms of PH (Ghofrani 2002: treatment group mean PAPs were 53 to 59mmHg; Ghofrani 2002a: 40mmHg). Bharani 2003 reported very high baseline mean PAP (80.78 (SD 21.3). Sastry 2004, reported particularly high baseline mean PAP of 107.36 (SD 24.98), and included only participants with a baseline mean PAP in excess of 30mm Hg.

Interventions

Two studies were short term (< 3 hours, Ghofrani 2002; Ghofrani 2002a). In these studies, the acute effects of treatment were assessed in the trials after an initial inhalation of NO. Ghofrani 2002 compared oral sildenafil in four treatment regimens: 12.5mg, 50mgs, 12.5mgs + inhaled iloprost and 50mgs + inhaled

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iloprost. Ghofrani 2002a compared oral sildenafil 50mgs versus IV epoprostenol. Sastry 2004 and Bharani 2003 assessed the effects of oral sildenafil compared with a placebo, for six and two week periods respectively, in addition to concomitant therapies such as digoxin and diuretics. Sastry 2004 also reported that oral anticoagulants were used at the physician's discretion. Co-interventions did not include other vasodilators in either study.

Setting

Ghofrani 2002 conducted the study in an ITU, Ghofrani 2002a did not report the setting of the trial. Sastry 2004 and Bharani 2003 were conducted in an outpatient setting.

Outcomes

Bharani 2003 reported change in NYHA functional class status. Ghofrani 2002; Ghofrani 2002a assessed the acute effects of sildenafil and focused on haemodynamic variables. Sastry 2004 and Bharani 2003 measured exercise capacity. Sastry 2004 assessed treatment effects in terms of the 'Chronic Heart Failure Questionnaire'. Sastry 2004 and Bharani 2003 measured symptoms and adverse effects.

Risk of bias in included studies

All studies with the exception of Bharani 2003 were well reported, and adequately randomised by computer generated randomisation schedules. However, in the two short term studies, blinding was not attempted. In clinical trials this may contribute to an overestimation of treatment effects, where there is subjective assessment of treatment effects, e.g. physician or patient rated clinical and/symptom scores. However, due to the short-term duration of the studies, this aspect may not have threatened internal validity. Due to the design of the two acute studies they have not measured longer term clinical symptoms, such as NYHA functional class status. The primary outcome of the review (change in NYHA functional class status), was measured in one study (Bharani 2003).

Effects of interventions

Oral sildenafil versus placebo (plus usual care) - crossover studies

Bharani 2003 (n=9, treatment period 2 weeks); Sastry 2004 (n=22, treatment period 6 weeks)

NYHA

Following treatment with sildenafil, Bharani 2003 reported that two participants improved their NYHA status by one class (no significant difference reported).

Quality of life

Total scores were not reported, but the findings from three domains of the CHFQ reported by Sastry 2004 were:

Dyspnoea: Significant difference in favour of sildenafil (21.95 (SD 6.02)) versus placebo (17.62 (SD 5.68)), P = 0.009.
Fatigue: Significant difference in favour of sildenafil (22.33 (4.82)) versus placebo (20.67 (SD 5.19)), P = 0.04.
Emotional function: No significant difference between sildenafil (37.33 (SD 9.32)) and placebo (34.71 (SD 10.91)), P = 0.06.

Borg scores

Bharani 2003 reported a significant difference in Borg breathlessness scores) (Scale 0 10) after the 6 minute walk test of 1.55 (P < 0.01)

Exercise capacity

This was measured by Sastry 2004 as time on treadmill. Participants were able to spend longer on the treadmill compared with placebo treatment (686.82 seconds (SD 224.02) versus 475.05 seconds (SD 168.02), P < 0.0001.

This was measured by Bharani 2003 as distance covered in a 6 minute walk test. Participants treated with sildenafil were able to walk further than those treated with placebo by 93.37metres (P < 0.005).

Haemodynamic variables

Data from Bharani 2003 and Sastry 2004 were pooled with a subgroup analysis by etiology (PPH versus mixed population studies). With a Fixed Effect model there was a significant reduction in mean PAP in favour of sildenafil of -11.14mmHg [-17.56, -4.72]. However, there was a significant level of heterogeneity (I^2 72.5%), and a Random Effects model gave a non-significant result (-12.76 [-25.7, 0.19]). The etiology of disease may not be the only variable to distinguish between these two studies. There were also different baseline arterial pressures in addition to different study duration and dosing regimens. In the absence of other studies, and the small sample sizes involved, the subgroup analysis is under-powered to provide useful insights into different responses to treatment.

Sastry 2004 reported a significant difference in cardiac index in favour of sildenafil (Sildenafil: 3.45 l/m^2 (SD 1.16) versus placebo: 2.80 (SD 0.90), P < 0.0001).

Adverse effects

A table of adverse effects is given in Table 2. No statistical analysis was undertaken on the difference in the side-effects in the study. No participants withdrew due to side-effects. One death occurred in the placebo group during the first arm of treatment.

High dose oral sildenafil versus low dose sildenafil with and without iloprost - parallel studies

Ghofrani 2002 (n=30, treatment duration single dose)

NYHA functional class status

No data on functional class status were reported

Haemodynamic variables

Data were presented on change from baseline scores for PVR, mean PAP, Cardiac Index and PVR/SVR. We have extracted data only for PVR as these were presented at equivalent time points (120 minutes). Data for all other variables were presented at 120 mins for sildenafil only treatment, and at 180 minutes for sildenafil plus additional iloprost inhalation. We entered data for the two sets of comparisons and stratified them on the basis of co-intervention. The trialists reported that combination therapy led to significant decrease in PVR compared with sildenafil alone (p < 0.001), and also to significant increase in cardiac index (p < 0.001). Data for all four treatment groups were presented in the original paper in graph format. These were extracted, entered and pooled by co-

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intervention to give a WMD in favour of high dose sildenafil of -15.86% (-30.64 to -1.08). The significant effect we observed in meta-analysis should be interpreted with caution due to the wide distribution of change scores in the study as a result of the small numbers.

Data on arterial oxygen saturation were not presented (non-significant differences reported).

Treatment effects for both single administration of sildenafil and combination therapy outlasted the observation periods of 120 minutes and 180 minutes respectively.

Safety

No adverse events were reported during combination therapy. No comment was made on the side-effects of single administration of sildenafil.

Oral sildenafil versus IV epoprostenol - parallel studies

Ghofrani 2002a (n=16, treatment duration- single dose)

NYHA

No data were reported on the effects of treatment on functional class status.

Haemodynamic variables

Epoprostenol (a prostaglandin analogue) caused a 42% median increase in cardiac index , compared with 9.1% in sildenafil treated patients (p = 0.002). Change in mean PAP and PVR did not differ significantly between the two groups (p = 0.054 and p = 0.197 respectively, no values are reported). Mean systematic arterial blood pressure was reduced by both treatments, but differed statistically between the groups in favour of sildenafil (p = 0.0005). However, no values were reported. Mean PaO2 differed significantly and was higher with sildenafil (p = 0.005, no values presented). Sildenafil also led to a higher, more favourable PVR/SVR ratio compared with prostacyclin (p = 0.02, no values were presented).

Treatment effects for sildenafil outlasted the observation period of 120-150 minutes.

Safety

No adverse events were reported during combination therapy

DISCUSSION

Four small studies have been included in this review. Due to the acute nature of two studies, and the limited assessment of functional class status in the remaining studies, firm conclusions regarding the effects of sildenafil on the course of PH are difficult to draw. Additionally, the participants in all the studies had very high pulmonary artery pressures, and in the case of Ghofrani 2002, were recruited in an ITU setting. Therefore they were representative of patients from the more severe end of the spectrum. Only one study explicitly recruited participants who conformed to the WHO 2001 classification of PH (Ghofrani 2002a). Whilst this classification may become more commonly used in clinical trials in PH, there is currently limited evidence in our review to draw a distinction between this diagnostic model and others such as functional status (NYHA), threshold blood pressure levels or even disease etiology.

The positive physiological effects observed in the acute studies require replication in larger and more rigorously controlled trials, but would indicate that there is a vasodilatory effect in PH when sildenafil is administered. Bharani 2003 and Sastry 2004 showed differences in terms of important outcomes such as symptoms and exercise capacity over two and six weeks. Nevertheless, these effects require confirmation on a larger scale, as well as its correlation with long term benefits including hospitalisation, mortality, and functional class status. Although Sastry 2004 reported mild side-effects, the study design and duration means that we cannot exclude the possibility that sildenafil may have long term side effects. Data from small non-randomised studies in people with PH have not found any systemic side-effects, such as visual disturbance, flushing, headache and dyspepsia (Ghofrani 2003; Kothari 2002) which have been reported in one large study of sildenafil for erectile dysfunction (Rosen 2003).

In an uncontrolled trial Ghofrani 2003 measured the effects of long term sildenafil treatment in addition to inhaled iloprost in severe pulmonary hypertension. The participants in the study were adults with mixed PH (PPH: N = 9, PH secondary to collagen vascular disease: N = 5), and were already deemed to have failed treatment with iloprost. After 12 months of additional sildenafil treatment improvements were noted in functional class status, exercise capacity and haemodynamic variables. Kothari 2002 also assessed long-term effects of sildenafil in paediatric and adult populations with mixed PH (PPH: N = 9, PH secondary to surgical correction of heart defect: N = 5). After a follow-up period of 7.3 months (SEM 2.4), improvements were observed in terms of NYHA status, exercise capacity and right ventricular systolic pressure. Findings from these studies indicate that randomised studies measuring similar outcomes are warranted. In such studies the etiology of the disease should be considered as a potential explanation for different responses to treatment, and ideally studies should be limited to specific diagnostic groups e.g. solely PPH.

AUTHORS' CONCLUSIONS

Implications for practice

Current evidence from randomised studies does not indicate whether long term administration of sildenafil in PH is justified. The studies have shown that there may be a vasodilatory effect either in combination or in comparison with inhaled iloprost in selected patients. Two small studies reported differences on exercise capacity and symptoms over two to six weeks, which require validation in larger studies. Further work is urgently required to establish that the short term effects observed in these patients can be replicated in larger, more representative and better defined patient samples, and that short term improvements in haemodynamic variables correlate with long term outcomes. A more adequate side-effect profile is also required.

Implications for research

Further studies are required and should take account of the following methodological and clinical considerations:

1. Adequate blinding of both study participant and trialist.
2. Trials should measure outcomes which are clinically relevant (e.g. mortality, NYHA functional class, hospitalisation) and which have been collected from adequate follow-up periods, so that long term effects can be established. Assessment of

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side-effects in larger samples of patients with PH would also be appropriate.

3. Disease etiology should be clearly described in future studies, and if possible data on participants with PPH and secondary PH should be analysed separately, to facilitate better identification of effects within these two subgroups.
4. Future studies should also assess the effects of treatment in less severe forms of PH.
5. To date the studies have recruited predominantly adult populations. The effects of sildenafil in children with PH needs also to be established.
6. Confirmatory studies are required to establish whether there is a dose response to sildenafil.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Bharani 2003

Methods	Randomised, double-blind, crossover study. Methods of randomisation: Not reported. Method of blinding: unclear. Withdrawals: N = 1. Jadad score: 3 (R: 1; B: 1; W: 1)

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Bharani 2003 *(Continued)*

	Statistical analysis: Paired t test.
Participants	N = 9 (5F). PPH: N = 3; PH secondary to ILD: N = 2; Thromboembolism: 1; Eisenmeger syndrome: Ventricular septal defect: N = 2; Patent ducus arteriosis: N = 1. NYHA status: II: N = 3; III: N = 5; IV: N = 1. Mean age: 32.11 (SD 15.06). Diagnosis established by clinical examination; routine lab evaluation; chest x-ray; ECG Inclusion criteria: NYHA >/= II; Doppler-estimated pulmonary systolic pressure: >/=35 mmHg; normal left ventricular function. Exclusion criteria: Reversible cause for PAH; contraindications for sildenafil therapy.
Interventions	Sildenafil 25mg 3 times per day versus placebo. Previous vasodilator therapy was withheld from 1 week to study entry. All other conventional therapy was maintained (warfarin; nifedipine; diuretics (N = 2); digoxin (N = 2). Study duration: 2 x 2 week treatment periods
Outcomes	6 minute walk test; change in symptoms; change in NYHA functional class; change in Borg; change in resting pulmonary artery systolic pressure.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Described as randomised, no other information available
Allocation concealment (selection bias)	Unclear risk	Information not available
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Placebo-controlled; uncertain of similarity between treatments.

Ghofrani 2002

Methods	Randomised, parallel group open label study. Methods of randomisation: Computer generated randomisation (blocks of 4). Blinding not undertaken. No withdrawals. Jadad score: 3 (R: 2; B: 0; W: 1)
Participants	N = 30 (23F). PPH: N = 10; Calcinosis: N = 6; chronic thromboembolic PH: N = 13; PH due to aplasia of left pulmonary artery: N = 1. NYHA: III or IV. Sildenafil 12.5: N = 7; Sildenafil 50: N = 8; Sildenafil 12.5 + iloprost: N = 7; Sildenafil 50 + iloprost: N = 8 Inclusion criteria: Mean PAP: >40 mm Hg; PH as defined by WHO World Symposium in PPH Exclusion criteria: PH secondary to COPD; pulmonary venous congestion; congenital heart disease; acute or chronic inflammatory lung disease; pregnancy or insufficient contraceptive methods; previous treatment with PDE inhibitors (including theophylline). Response to NO was recorded, but was not an inclusion nor an exclusion criterion.
Interventions	All participants had inhaled NO. Subsequently they were randomised to one of the following treatment groups:

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Ghofrani 2002 *(Continued)*

	Sildenafil 12.5 mg Sildenafil 50 mg Sildenafil 12.5 mg + iloprost Sildenafil 50 mg plus iloprost. Study duration: 120 minutes for participants receiving sildenafil alone; 180 minutes for participants receiving sildenafil plus iloprost
Outcomes	Arterial pressure; cardiac output; central venous pressure; peripheral oxygen saturation; blood gases;
Notes	No blinding undertaken. Short term study assessing the acute effects of sildenafil alone or in combination with iloprost. No assessment of safety undertaken/possible due to the short term nature of the study. Mixed population. Trialists undertook subgroup analysis - no significant difference in response to treatment determined by type of PH.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer generated randomisation (blocks of 4)
Allocation concealment (selection bias)	Unclear risk	Information not available
Blinding (performance bias and detection bias) All outcomes	High risk	Open label trial

Ghofrani 2002a

Methods	Randomised, open label parallel group trial. Patients were randomised by computer in blocks of four. Blinding not possible. No participants withdrew. Jadad score: 3 (R: 2; B: 0; W: 1)
Participants	Eligible: 25; N = 16. Mean age: 56.5 years (27 to 79); mean PAP: 40 mm Hg (25 to 62); Cardiac Index: 2.3 L/min/m2 (1.2 to 4.3); PVR: 1108.7 dyne/s/cm-5/m2 (448 to 3296); PaO2: 73.5 mm Hg (52 to 104); NYHA status: III (N = 10); IV: (N = 6) Inclusion criteria: Lung fibrosis defined by ATS and ERS guidelines; severe PH (mean PAP >35 mm Hg) Exclusion criteria: Pulmonary venous PH (pulmonary arterial wedge pressure >15 mm Hg); underlying lung disease other than fibrosis (COPD; recurrent PE); prior treatment with theophyllines
Interventions	All participants inhaled NO prior to randomisation. Participants were randomised to IV iloprost (epoprostenol given in doses increased by 2 ng/kg/min) or oral sildenafil 50 mg Study duration: 60 minutes
Outcomes	PVR; mean PAP; pulmonary shunt flow; PaO2; cardiac output; adverse effects (short term)
Notes	Short term study assessing the acute effects of sildenafil versus epoprostenol in terms of haemodynamic variables. No blinding undertaken.

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Ghofrani 2002a *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer generated randomisation
Allocation concealment (selection bias)	Unclear risk	Information not available
Blinding (performance bias and detection bias) All outcomes	High risk	Open label trial

Sastry 2004

Methods	Randomised, double-blind, crossover study. Method of randomisation: computer generated random numbers. Blinding: unclear. Withdrawals: N = 2. ITT analysis. Jadad score: 4 (R: 2, B: 1, W:1). Statistical analysis: Paired t test.
Participants	N = 22. Age range: 16-55 years; mean PAP: > 30 mmHg (mean not reported); Cardiac Index (L/m2): 2.83 (SD 1.06); Pulmonary artery systolic pressure (mmHg) 107.36 (SD 24.98); NYHA status: II (N = 18); III (N = 4); Quality of Life (CHFQ): Dyspnoea: 21.86 (SD 6.47); Fatigue: 20.38 (SD 5.12); Emotional function: 34.14 (SD 10.38) Inclusion criteria: 12-65 years of age; NYHA II & III; estimated PAP >30mmHg; able to walk on a treadmill Exclusion criteria: NYHA I or IV; significant r-to-l shunt; valvular heart disease; left ventricular systolic dysfunction; systemic hypertension; secondary pulmonary hypertension; severe co-morbid conditions
Interventions	Oral sildenafil versus placebo. Participants could not use other vasodilators. Digoxin, diuretics and oral anticoagulants were used at clinician's discretion. Dosage varied according to body weight (0-25kg, 3x25mg per day; 26-50kg, 3x50mg per day; >51kg, 100mg 3x100 per day) Study duration: 6 weeks. No washout phase was undertaken
Outcomes	Exercise capacity; Quality of life (dyspnoea, emotion, fatigue); change in pulmonary artery systolic pressure; cardiac output; adverse events
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer generated random numbers
Allocation concealment (selection bias)	Unclear risk	Information not available
Blinding (performance bias and detection bias)	Unclear risk	Placebo-controlled; uncertain of similarity between treatments.

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Sastry 2004 *(Continued)*
All outcomes

CHFQ: Chronic heart failure questionnaire; COPD: chronic obstructive pulmonary disease; Jadad scores: R: Randomisation; B: Blinding: W: Withdrawals; NO: Nitric oxide; NYHA: New York Heart Association Funcional Class Status; PAP: pulmonary arterial pressure; PVR: Pulmonary vascular resistance; PH: Pulmonary hypertension; PPH: Primary pulmonary hypertension; ILD: Interstitial Lung Disease

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Anonymous 2001	Before and after study in healthy volunteers who had breathed in low levels of oxygen to induce 'pulmonary hypertension'.
Anonymous 2001a	Review article on pulmonary hypertension in neonates
Channick 2001	Review article
Chockalingam 2005	Before and after study
Deeb 1989	Retrospective analysis of amrinone therapy in patients with pulmonary hypertension
Dweik 2002	Review article
Ewert 2003	Correspondence in response to a non-randomised study.
Frost 2005	Study of endothelin
Ghofrani 2003	Before and after study.
Ghofrani 2004	Healthy volunteers
Hoeper 2003	Review article
Humpl 2005	Before and after study
Ikeda 2005	Observational study
Kothari 2002	Before and after study of sildenafil administered to 14 people with PAH.
Kulkarni 1996	Randomised controlled trial comparing the effects of oxygen, sublingual isosorbide dinitrate, IV aminophylline, and sublingual nifedipine. Sildenafil was not administered.
Lepore 2002	Non-randomised prospective observational study.
Machado 2005	Before and after study
McKay 1989	Before and after study in 10 patients with pulmonary hypertension.
Michelakis 2002	Before and after study
Richalet 2004	Healthy volunteers
Richalet 2005	Healthy volunteers

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Study	Reason for exclusion
Schmid 1999	Randomised controlled trial examining the effects of iNO (inhaled nitric oxide) in post-operative with severe PH post-operative in comparison with IV vasodilators. Excluded as neither of the two vasodilators used as comparators were sildenafil.
Wilkens 2001	Before and after study
Wilkins 2005	Comparison of sildenafil and endothelin
Zhao 2001	Animal study.

IV: Intravenous

DATA AND ANALYSES

Comparison 1. Oral sildenafil versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Improvement in NYHA status - post treatment in crossover studies	1		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
2 Exercise time on treadmill - crossover studies	1		Seconds (Fixed, 95% CI)	Totals not selected
3 Exercise time on treadmill - 1st arm/parallel studies	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
4 Exercise capacity - 6 minute walk test - crossover studies	1		Metres (Fixed, 95% CI)	Totals not selected
5 Cardiac index - crossover studies	1		L/m2 (Fixed, 95% CI)	Totals not selected
6 Pulmonary artery systolic pressure - crossover studies	2	58	mmHg (Fixed, 95% CI)	-11.14 [-17.56, -4.72]
6.1 Primary pulmonary hypertension	1	40	mmHg (Fixed, 95% CI)	-6.73 [-14.59, 1.13]
6.2 Mixed population studies	1	18	mmHg (Fixed, 95% CI)	-20.0 [-31.13, -8.87]
7 Borg dyspnea score - crossover studies	1		Borg (Fixed, 95% CI)	Totals not selected
8 Quality of life: dyspnoea - crossover studies	1		CHFQ score (Fixed, 95% CI)	Totals not selected
9 Quality of life: fatigue - crossover studies	1		CHFQ score (Fixed, 95% CI)	Totals not selected
10 Quality of life - emotional function (crossover studies)	1		CHFQ score (Fixed, 95% CI)	Totals not selected

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Analysis 1.1. Comparison 1 Oral sildenafil versus placebo, Outcome 1 Improvement in NYHA status - post treatment in crossover studies.

Study or subgroup	Sildenafil n/N	Placebo n/N	Odds Ratio M-H, Fixed, 95% CI	Odds Ratio M-H, Fixed, 95% CI
Bharani 2003	2/9	0/9		6.33[0.26,152.86]

Favours treatment 0.005 0.1 1 10 200 Favours control

Analysis 1.2. Comparison 1 Oral sildenafil versus placebo, Outcome 2 Exercise time on treadmill - crossover studies.

Study or subgroup	Sildenafil N	Placebo N	Seconds (SE)	Seconds IV, Fixed, 95% CI	Seconds IV, Fixed, 95% CI
Sastry 2004	20	20	211.7 (29.55)		211.7[153.78,269.62]

Placebo better -1000 -500 0 500 1000 Sildenafil better

Analysis 1.3. Comparison 1 Oral sildenafil versus placebo, Outcome 3 Exercise time on treadmill - 1st arm/parallel studies.

Study or subgroup	Sildenafil N	Sildenafil Mean(SD)	Placebo N	Placebo Mean(SD)	Mean Difference Fixed, 95% CI	Mean Difference Fixed, 95% CI
Sastry 2004	10	698.1 (272.9)	12	452.1 (165.6)		246[52.64,439.36]

Favours placebo -1000 -500 0 500 1000 Favours sildenafil

Analysis 1.4. Comparison 1 Oral sildenafil versus placebo, Outcome 4 Exercise capacity - 6 minute walk test - crossover studies.

Study or subgroup	Sildenafil N	Placebo N	Metres (SE)	Metres IV, Fixed, 95% CI	Metres IV, Fixed, 95% CI
Bharani 2003	9	9	93.4 (26.54)		93.37[41.35,145.39]

Favours treatment -100 -50 0 50 100 Favours control

Analysis 1.5. Comparison 1 Oral sildenafil versus placebo, Outcome 5 Cardiac index - crossover studies.

Study or subgroup	Sildenafil N	Placebo N	L/m2 (SE)	L/m2 IV, Fixed, 95% CI	L/m2 IV, Fixed, 95% CI
Sastry 2004	20	20	0.7 (0.124)		0.65[0.41,0.89]

Placebo better -10 -5 0 5 10 Sildenafil better

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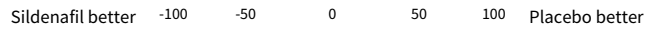
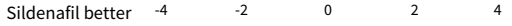
Analysis 1.6. Comparison 1 Oral sildenafil versus placebo, Outcome 6 Pulmonary artery systolic pressure - crossover studies.

Study or subgroup	Sildenafil N	Placebo N	mmHg (SE)	mmHg IV, Fixed, 95% CI	Weight	mmHg IV, Fixed, 95% CI
1.6.1 Primary pulmonary hypertension						
Sastry 2004	20	20	-6.7 (4.01)		66.74%	-6.73[-14.59,1.13]
Subtotal (95% CI)					**66.74%**	**-6.73[-14.59,1.13]**
Heterogeneity: Not applicable						
Test for overall effect: Z=1.68(P=0.09)						
1.6.2 Mixed population studies						
Bharani 2003	9	9	-20 (5.68)		33.26%	-20[-31.13,-8.87]
Subtotal (95% CI)					**33.26%**	**-20[-31.13,-8.87]**
Heterogeneity: Not applicable						
Test for overall effect: Z=3.52(P=0)						
Total (95% CI)					**100%**	**-11.14[-17.56,-4.72]**
Heterogeneity: Tau^2=0; Chi^2=3.64, df=1(P=0.06); I^2=72.55%						
Test for overall effect: Z=3.4(P=0)						
Test for subgroup differences: Chi^2=3.64, df=1 (P=0.06), I^2=72.55%						



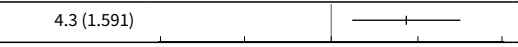
Analysis 1.7. Comparison 1 Oral sildenafil versus placebo, Outcome 7 Borg dyspnea score - crossover studies.

Study or subgroup	Sildenafil N	Placebo N	Borg (SE)	Borg IV, Fixed, 95% CI	Borg IV, Fixed, 95% CI
Bharani 2003	9	9	-1.5 (0.491)		-1.55[-2.51,-0.59]



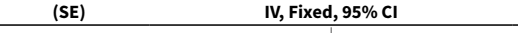
Analysis 1.8. Comparison 1 Oral sildenafil versus placebo, Outcome 8 Quality of life: dyspnoea - crossover studies.

Study or subgroup	Sildeanfil N	Placebo N	CHFQ score (SE)	CHFQ score IV, Fixed, 95% CI	CHFQ score IV, Fixed, 95% CI
Sastry 2004	20	20	4.3 (1.591)		4.33[1.21,7.45]



Analysis 1.9. Comparison 1 Oral sildenafil versus placebo, Outcome 9 Quality of life: fatigue - crossover studies.

Study or subgroup	Sildenafil N	Placebo N	CHFQ score (SE)	CHFQ score IV, Fixed, 95% CI	CHFQ score IV, Fixed, 95% CI
Sastry 2004	1	1	1.7 (0.808)		1.66[0.08,3.24]



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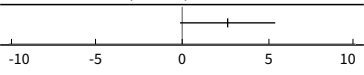
Analysis 1.10. Comparison 1 Oral sildenafil versus placebo, Outcome 10 Quality of life - emotional function (crossover studies).

Study or subgroup	Sildenafil N	Placebo N	CHFQ score (SE)	CHFQ score IV, Fixed, 95% CI	CHFQ score IV, Fixed, 95% CI
Sastry 2004	20	20	2.6 (1.401)		2.62[-0.12,5.36]

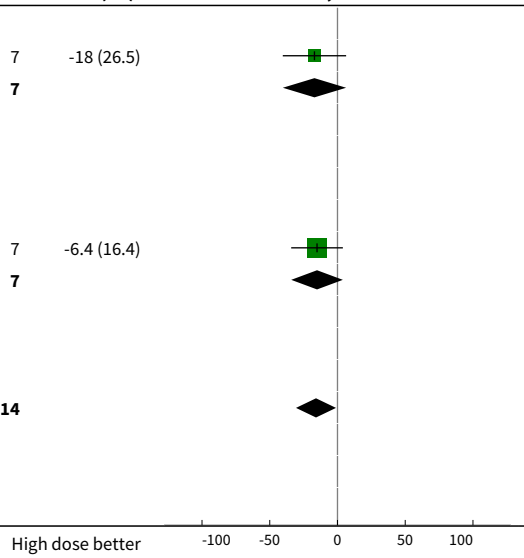


Comparison 2. High dose oral sildenafil versus low dose oral sildenafil

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Change in pulmonary vascular resistance	1	30	Mean Difference (IV, Fixed, 95% CI)	-15.86 [-30.64, -1.08]
1.1 Sildenafil plus iloprost	1	15	Mean Difference (IV, Fixed, 95% CI)	-17.0 [-40.38, 6.38]
1.2 Sildenafil alone	1	15	Mean Difference (IV, Fixed, 95% CI)	-15.1 [-34.17, 3.97]

Analysis 2.1. Comparison 2 High dose oral sildenafil versus low dose oral sildenafil, Outcome 1 Change in pulmonary vascular resistance.

Study or subgroup	High dose N	High dose Mean(SD)	Low dose N	Low dose Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
2.1.1 Sildenafil plus iloprost							
Ghofrani 2002	8	-35 (18.4)	7	-18 (26.5)		39.96%	-17[-40.38,6.38]
Subtotal ***	**8**		**7**			**39.96%**	**-17[-40.38,6.38]**
Heterogeneity: Not applicable							
Test for overall effect: Z=1.43(P=0.15)							
2.1.2 Sildenafil alone							
Ghofrani 2002	8	-21.5 (21.2)	7	-6.4 (16.4)		60.04%	-15.1[-34.17,3.97]
Subtotal ***	**8**		**7**			**60.04%**	**-15.1[-34.17,3.97]**
Heterogeneity: Not applicable							
Test for overall effect: Z=1.55(P=0.12)							
Total ***	**16**		**14**			**100%**	**-15.86[-30.64,-1.08]**
Heterogeneity: Tau²=0; Chi²=0.02, df=1(P=0.9); I²=0%							
Test for overall effect: Z=2.1(P=0.04)							
Test for subgroup differences: Chi²=0.02, df=1 (P=0.9), I²=0%							



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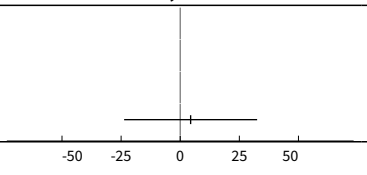
Comparison 3. Oral sildenafil versus prostacyclin

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Change in pulmonary vascular resistance	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
1.1 Low dose sildenafil	0		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
1.2 High dose sildenafil	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]

Analysis 3.1. Comparison 3 Oral sildenafil versus prostacyclin, Outcome 1 Change in pulmonary vascular resistance.

Study or subgroup	Sildenafil N	Sildenafil Mean(SD)	Iloprost N	Iloprost Mean(SD)	Mean Difference Fixed, 95% CI	Mean Difference Fixed, 95% CI
3.1.1 Low dose sildenafil						
3.1.2 High dose sildenafil						
Ghofrani 2002	8	-32.5 (25.4)	8	-36.9 (31.7)		4.4[-23.72,32.52]



ADDITIONAL TABLES

Table 1. Seach update detail

Search date	Articles retrieved	N assessed	Unique studies	Included	Excluded
October 2004-5	285	8	8	0	8 (observational study/before and after study: 3; Healthy volunteers: 3; RCT of wrong comparison: 1; study of ERAs: 1)
October 2005-6	396	19	17		

Table 2. Adverse effects in Sastry 2004

Effect	Sildenafil (N/22)	Placebo (N/22)
Body aches	1	2
Backache	3	1
Headache	3	1
Insomnia	2	3
Leg pains	3	6

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Table 2. Adverse effects in Sastry 2004 *(Continued)*

Numbness of hands & feet	4	1
Anorexia	3	3
Nausea & vomiting	1	5
Abdominal discomfort	3	6
Constipation	3	0
Giddiness	1	4
Syncope	0	1
Death	0	1

APPENDICES

Appendix 1. MEDLINE search strategy

(combined with RCT filter outlined in Group Module)

1 exp Hypertension, Pulmonary/
2 (pulmonary adj5 hypertens$).mp. [mp=title, original title, abstract, name of substance, mesh subject heading]
3 1 or 2
4 exp Vasodilator Agents/
5 [exp VASODILATION/de [Drug Effects]]
6 (viagra or sildenafil).mp. [mp=title, original title, abstract, name of substance, mesh subject heading]
7 exp Phosphodiesterase Inhibitors/
8 PDE5.mp.
9 4 or 5 or 6 or 7 or 8
10 3 and 9

Appendix 2. EMBASE search strategy

(combined with RCT filter outlined in Group Module)

1. exp Pulmonary Hypertension/
2. (pulmonary adj5 hypertens$).mp. [mp=title, abstract, subject headings, drug trade name, original title, device manufacturer, drug manufacturer name]
3. 1 or 2
4. exp Vasodilator Agent/
5. exp Vasodilatation/
6. exp Sildenafil/
7. sildenafil.mp.
8. viagra.mp.
9. exp Phosphodiesterase Inhibitor/
10. PDE5.mp. [mp=title, abstract, subject headings, drug trade name, original title, device manufacturer, drug manufacturer name]
11. 4 or 5 or 6 or 7 or 8 or 9 or 10
12. 3 and 11

Appendix 3. CENTRAL search strategy

#1. HYPERTENSION PULMONARY explode tree 1 (MeSH)
#2. (pulmonary near hypertens*)
#3. (#1 or #2)
#4. VASODILATOR AGENTS explode tree 1 (MeSH)
#5. VASODILATION [de] single term (MeSH)

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#6. PHOSPHODIESTERASE INHIBITORS single term (MeSH)
#7. pde5
#8. (viagra or sildenafil)
#9. (#4 or #5 or #6 or #7 or #8)
#10. (#9 and #3)

WHAT'S NEW

Date	Event	Description
26 February 2019	Review declared as stable	This review has been superseded by http://dx.doi.org/10.1002/14651858.CD012621.pub2

HISTORY

Protocol first published: Issue 3, 2001
Review first published: Issue 4, 2004

Date	Event	Description
5 June 2014	Amended	Title and PLS title amended
15 August 2008	Amended	Converted to new review format.
2 October 2006	New search has been performed	Literature search re-run, no new studies found
1 August 2004	New citation required and conclusions have changed	Substantive amendment

CONTRIBUTIONS OF AUTHORS

PK: Initiation of the review, study assessment, data extraction and entry, interpretation
TJL: Study assessment, data extraction and entry, analysis, interpretation
EHW: Content supervision, interpretation and editorial support

DECLARATIONS OF INTEREST

None known.

SOURCES OF SUPPORT

Internal sources

- Division of Community Health Sciences, St George's, University of London, UK.

External sources

- No sources of support supplied

NOTES

This review has been superseded by http://dx.doi.org/10.1002/14651858.CD012621.pub2

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INDEX TERMS

Medical Subject Headings (MeSH)

3',5'-Cyclic-GMP Phosphodiesterases [*antagonists & inhibitors]; Hypertension, Pulmonary [*drug therapy]; Piperazines [*therapeutic use]; Purines; Randomized Controlled Trials as Topic; Sildenafil Citrate; Sulfones; Vasodilator Agents [*therapeutic use]

MeSH check words

Humans

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